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Review

Role of NF-κB in thyroid cancer

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ABSTRACT

Thyroid cancer is the most common neoplasia of the endocrine system and accounts for approximately 1% of all newly diagnosed cancer cases. Its incidence has rapidly grown over the past few decades. Although most thyroid carcinomas are of the well-differentiated papillary histology, and respond well to treatment with surgical resection followed by radioactive iodine ablation, tumors with more aggressive phenotype, such as follicular, poorly differentiated, anaplastic, and medullary cancers, lead to almost 1500 patient deaths annually. Therefore, understanding molecular mechanisms that regulate the biology of these carcinomas could be helpful to identify new molecules acting as novel targets for therapeutic intervention.

NF-κB has been recently shown to play an important role in thyroid cancer for its ability to control the proliferative and the anti-apoptotic signaling pathways of thyroid neoplastic cells. Oncogenic proteins RET/PTC, RAS and BRAF, that are involved in many aspects of thyroid carcinogenesis, can induce NF-κB activation in papillary, follicular, and medullary thyroid carcinomas, while constitutive de-regulated NF-κB activity has been found in anaplastic thyroid carcinomas. A number of NF-κB inhibitors have been demonstrated to induce anti-proliferative effects and/or massive apoptosis, especially in combination with radio- or chemo-therapy. The results obtained suggest that targeting NF-κB could be a promising strategy for advanced thyroid cancer treatment.

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Abbreviations: NF-κB, nuclear factor-kappa B; IκB, inhibitor of NF-κB; IKK, IκB Kinase; TNF, tumor necrosis factor; IAP, inhibitor of apoptosis; c-FLIP, cellular FADD-like interleukin 1beta converting enzyme inhibitory protein; GADD, growth arrest and DNA damage; NEMO, NF-κB essential modulator; TRAIL, TNF-related apoptosis-inducing ligand; PTEN, phosphatase and tensin homologue; JNK, Jun N-terminal kinase; ROS, reactive oxygen species; LTβ-R, lymphotoxin beta-receptor; BAFF-R, B cell activation factor from the TNF family-receptor; NGAL, neutrophil gelatinase-associated lipocalin; PPARγ, peroxisome proliferator-activated receptor gamma; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; ATC, anaplastic thyroid carcinoma.

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1. Introduction

Thyroid carcinomas mainly comprise four types of tumors: papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), both of which may be summarized as differentiated thyroid carcinoma, medullary thyroid carcinoma (MTC), and undifferentiated anaplastic thyroid carcinoma (ATC). PTC, FTC and ATC derive from the thyroid follicular epithelial cells, while MTC derives from the parafollicular C-cells (Sherman, 2003). PTC is the most common malignant thyroid neoplasm in countries with sufficient iodine diets, and comprises up to 80% of all thyroid malignancies. FTC is more common in regions with insufficient iodine diets and represents approximately 10–20% of all thyroid malignancies (Fagin and Mitsiades, 2008). The overall 5–10-year survival rate of patients with PTC is about 80–95%, while that of patients with FTC is about 70–95% (Gimm, 2001). The incidence of MTC is not well known because epidemiologic studies are rare. Generally, it is believed that MTC comprises about 5–10% of all thyroid malignancies (Gimm, 2001; Sherman, 2003). ATC is one of the most aggressive human malignancies, with a very poor prognosis. Although rare, accounting for up to 1–2% of clinically recognized thyroid cancers, the overall median survival is limited to months (Smallridge et al., 2009). Unfortunately, at the time of diagnosis most of ATC patients already show local and distant metastases, so that surgery, radio-therapy, and chemo-therapy, based primarily on doxorubicin and cisplatin treatment, do not meaningfully improve survival of these patients. Consequently, there is a need for new diagnostic and therapeutic tools for the treatment of these tumors.

An emerging body of literature shows that NF-κB plays a role in thyroid cancer (Visconti et al., 1997; Ludwig et al., 2001; Russell et al., 2003; Vasudevan et al., 2004; Kato et al., 2006; Palona et al., 2006; Gombos et al., 2007; Gallel et al., 2008), especially of anaplastic type (Pacifico et al., 2004, 2007; Starenki et al., 2004a; Iannetti et al., 2008; Festa et al., 2009; Zhu et al., 2009). This is an important issue because NF-κB, and particularly the genes under its transcriptional regulation, could potentially become novel molecular targets in ATC therapy, given the ability of NF-κB to control many aspects of thyroid cancer biology. This review will focus on these aspects, in particular on the molecular mechanisms by which NF-κB exerts its role in thyroid tumors.

2. NF-κB

NF-κB is a family of transcription factors that plays a central role in the regulation of apoptosis, inflammation and immune response (Ghosh et al., 1998; Karin and Ben-Neriah, 2000; Tak and Firestein, 2001). In mammals, the NF-κB family is composed of five members: RelA(p65), RelB, c-Rel, NF-κB1 (p50 and its precursor p100), NF-κB2 (p52 and its precursor p105) (Vallabhapurapu and Karin, 2009). These proteins form homodimers and heterodimers and their activity is regulated by two major pathways. The first pathway – known as the canonical pathway – regulates the activity of NF-κB dimers composed of RelA(p65), c-Rel and p50. These dimers are held in the cytoplasm in an inactive form bound to specific inhibitors known as inhibitor of κB (IκB). Following different stimuli, such as cytokines, pathogens and pathogen-related factors, IκB is phosphorylated on specific serine residues, ubiquitinated and degraded through a proteasome dependent pathway. NF-κB dimers are then free to move to the nucleus and to transcribe target genes (Hayden and Ghosh, 2008). The second pathway affects NF-κB2, which preferentially dimerizes with RelB. Following triggering of some members of the TNF receptor superfamily, such as LTβ-R and BAFF-R, NF-κB2 is phosphorylated, ubiquitinated, and processed to form the mature form p52. RelB-p52 dimers

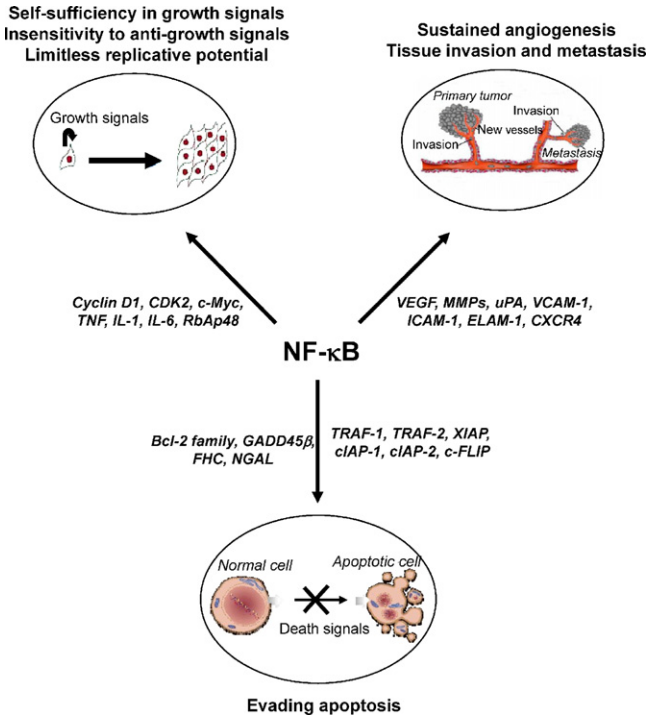

Fig. 1. NF-κB contributes to cancer development through regulation of different genes involved in oncogenesis. According to Hanahan and Weinberg, six essential alterations in cell physiology characterize a tumor cell: self-sufficiency in growth, insensitivity to growth-inhibitory signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis and tissue invasion and metastasis. Many of the genes able to mediate such effects are under transcriptional control of NF-κB.

then move to the nucleus, where they control transcription of genes involved in secondary lymphoid organ development and lymphocytes survival (Claudio et al., 2002; Kayagaki et al., 2002; Dejardin et al., 2002). The phosphorylation of the IκB and NF-κB2 is mediated by a high molecular weight complex, the IκB Kinase (IKK) complex. This complex is composed by two catalytic subunits, IKKα and IKKβ, and a regulatory subunit IKKγ/NEMO (Ghosh and Karin, 2002). IKKα and IKKβ have distinct substrates. IKKβ directly phosphorylates IκB, then activating the canonical pathway, while IKKα mediates the phosphorylation of NFκB2 along with another protein kinase called NIK (Xiao et al., 2001; Senftleben et al., 2001). IKKγ/NEMO does not have any enzymatic activity but its presence in the complex is absolutely necessary for a correct activation of the IKK complex, very likely because it serves to connect upstream signal mediators to the IKK (Yamaoka et al., 1998; Rothwarf et al., 1998). Once in the nucleus, NF-κB transcribes different genes controlling different aspects of cell physiology. Since many of these genes fall in the six categories characterizing a neoplastic cell ((1) self-sufficiency in growth, (2) insensitivity to growth-inhibitory signals, (3) evasion of apoptosis, (4) limitless replicative potential, (5) sustained angiogenesis and (6) tissue invasion and metastasis) (Hanahan and Weinberg, 2000), it is not surprising that the NF-κB pathway is involved in cell transformation (Fig. 1).

No information is available about the role played by NF-κB in thyroid gland development, and very little is known about the influence of NF-κB on the regulation of thyroid functions, as well as on the expression of thyroid specific genes, such as thyroglobulin, thyroid stimulating hormone-receptor, and thyroperoxidase. It has been reported that the murine Pax8 gene contains κB sites, however no experimental evidence confirmed that theses sites are functional (Okladnova et al., 1997).

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